REMARKS

The examiner has rejected claims 1, 2, 7-9, 12-15, 17, 19, and 20. Claims 1-20 are pending. Claims 3-6, 10, 11, 16 and 18 are withdrawn from consideration as being directed to a non-elected invention. Claim 2 is identified as withdrawn herein in view of the election of Group V (subject to the interpretation "peptide comprising the PXP motif").

Claim 2 is amended to delete the subject matter currently examined, thus leaving the phrases "wherein the Vif antagonist is an anti-Vif antibody" and "a Vif protein fragment which comprises at least SEQ ID NO: 25" remaining in the claim. In view of the non-elected subject matter remaining in claim 2, claim 2 is designated herein as "withdrawn" from consideration.

Claim 7 is canceled in view of the inclusion of the limitations of claim 7 into claim 1.

Claims 1, 8 and 12, and 15 are amended to be consistent with the restriction requirement.

Claim 9 is amended to correct a minor grammatical error.

Claims 12-15 are amended to change the term "peptides" to the singular corresponding to the antecedent basis in claim 1 using "peptide" in the singular. No change of scope is thereby intended as the singular forms is intended to include plural referents.

Claims 21 and 22 are new, and are directed to the embodiment of the invention where the peptide comprises or consists of the sequence SEQ ID NO. 11.

The claims are amended without prejudice to, or disclaimer of, the cancelled subject matter. Applicants reserve the right to pursue the canceled subject matter in one or more continuing or divisional applications. The amendments are not believed to add new matter and entry is respectfully requested.

Response to the rejection under the 35 U.S.C. § 112, first paragraph, written description requirement

The examiner rejected claims 1, 2, 7-9, 12-15, 17, 19, and 20 under 35 U.S.C. § 112, first paragraph, written description requirement. The applicant respectfully traverses the rejection.

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed and the examiner has the burden of presenting evidence or reasons why persons skilled in the persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. MPEP 2163(I)(A) (citing *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976)).

The examiner states that applicants' written description is inadequate. Specifically, the examiner claims that "[a]pplicants' specification leads one to believe that applicant was in possession of only SEQ ID NO: 11 and not all antagonists that bind to Vif." Office Action at 3. The examiner alleges that the specification does not recite a number of peptides or non-peptide inhibitors or mimetics in order to define what falls within the scope of the claimed genus of "Vif antagonists" and therefore the skilled artisan cannot envision the detailed structure of the encompassed genus of Vif antagonists. Office Action at 4-5.

By stating the applicants only "possessed" SEQ ID 11, and not all Vif antagonists, the examiner appears to suggest that in order to meet the written description requirement the applicants would have to have physical possession of every possible embodiment of the claim, and enumerate every possible embodiment of the same in the specification. However, this is not is what is required under the written description requirement. Rather, what is required is an adequate description of the invention. MPEP 2163(I)(A).

Contrary to the examiner's arguments, Applicants were in possession of the invention at the time the claimed invention was made. However, without acquiescing to the propriety of the rejection, claim 1 as newly amended herein now claims a Vif antagonist which is a peptide

comprising a PXP motif. The amendment incorporates the limitations of former claim 7 into claim 1, and the applicant respectfully submits that the amendment overcomes the rejection. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

The person skilled in the art can readily envision what is claimed by amended claim 1, namely a method of inhibiting Vif multimerization by administering a Vif antagonist which is a peptide comprising the PXP motif. The specification adequately describes what is meant by "Vif multimerization" and a "Vif antagonist. Likewise, the specification adequately describes the Vif antagonists that may be used in the method of the invention as a defined class of compounds, namely peptides that comprise the specific PXP motif. While it is recognized that a claim to a method treatment with a compound having properties without any indication in the specification of the structure of compounds which would have the desired properties may fail to meet the written description requirement (see, e.g. *University of Rochester v. G.D. Searle & Co.*, 69 U.S.P.Q.2d 1886, 1890 (Fed. Cir. 2004), that is not the case presented by the present application.

Applicants have described the essential structural feature of the compounds to be used in invention. Specifically, applicants have identified peptides comprising the PXP motif as being effective as Vif antagonists. Applicants limit their claims to the method comprising peptides comprising the PXP motif. The claims thus embody a precise definition of the compounds that are effective in carrying out the method of the invention. The examiner states that the PXP motif may be necessary, but is not necessarily sufficient to carry out the method of the invention. The examiner has not, however, provided any evidence or reasons to support this assertion, and attempts to shift back to the applicant the burden of disproving the assertion that the written description is inadequate. Even assuming, arguendo, that some peptides bearing the PXP motif were not useful in carrying out the method of the invention, it is well established that the existence of some inoperative embodiments within the scope of the claims does not defeat patentability. The requirement in the claims that the PXP-motif-containing peptide also be a Vif antagonist provides an additional level of characterization, for which methods are described in

the specification, which yet further enhances the adequacy of the written description of applicants' invention.

Applicants have provided precisely what the examiner suggests should be required to meet the written description requirement, namely description of a representative number of PXP species having the requisite properties for carrying out the method of the invention. The specification demonstrates that peptides comprising a PXP motif serve as Vif antagonists by binding to the Vif multimerization domain. The specification (Table 1, p. 35) demonstrates that all the following peptides, each of which shares the PXP motif, inhibit Vif-Vif interaction, and thus Vif multimerization:

SQ ID NO.	Peptide
9	SVSVGMKPSPRP
11	SNQDDSPLPRSV
13	LPLPAPSFHRTT
21	KPKKIKPPLPSV
22	PPLPSVTKLTEDRWN
23	KKIKPPLPSVTKLTE

The specification discloses that peptides comprising the PXP motif are capable of binding HIV-1 Vif protein at high affinity (specification, p. 33, lines 22-27.) Peptides containing the PXP motif (SEQ ID NOs: 9, 11 and 13) were demonstrated to inhibit Vif-Vif interactions (p. 33, lines 29-31). Additional PXP motif-containing peptides comprising Vif fragments (SEQ ID NOs: 21, 22, and 23) were also demonstrated to inhibit Vif-Vif interactions (Table 1).

The specification therefore teaches that peptides containing the PXP-motif, particular the P*L*P motif (SEQ ID NOs: 11, 13, 21, 22 and 23) are capable of inhibiting Vif-Vif interaction required for Vif multimerization. The specification teaches that the peptides function by binding to the ^{161}PPLP^{164} site within the Vif protein which comprising the Vif multimerization

domain. The peptides for evaluation were generated by random mutagenesis, then selected for the presence of the PXP motif. Other PXP-containing peptides were generated as fragments of the Vif protein containing the ^{161}PPLP^{164} motif. The PXP-containing peptides were demonstrated to block the multimerization of Vif through biding to the ^{161}PPLP^{164} site on the Vif protein. By interfering with Vif multimerization, the PXP-containing peptides inhibit HIV-1 infection, since Vif function is essential in the HIV-1 life cycle. This is demonstrated by the fact that a mutant which lacks the Vif multimerization domain is unable to rescue the infectivity of Vif-defective viruses (p. 32, line 25 – page 33, line 19).

In view of the teachings of the specification, one skilled in the art would conclude that applicant was in possession of the claimed method for inhibiting Vif multimerization in a subject through administration of peptide comprising a PXP motif. The specification discloses several peptides that are capable of inhibiting Vif-Vif interaction. The specification describes two sources of additional peptides: (1) fragmentation of Vif, and isolation of peptides containing the ^{161}PPLP^{164} sequence, or (2) random mutagenesis and selection of PXP-containing small peptides. The specification provides assays for assessing Vif-Vif interactions, which can be used to confirm the impact of any PXP-containing peptide on Vif multimerization. The specification demonstrates no fewer than 6 peptides that are effective in inhibiting inhibit Vif-Vif interactions.

Based on the foregoing, the rejection under the enablement requirement is believed to have been overcome. The applicant therefore respectfully requests reconsideration and withdrawal of the rejection under the 35 U.S.C. § 112, first paragraph, written description requirement.

Response to the rejection under the under the 35 U.S.C. § 112, first paragraph, enablement requirement

The examiner rejects claims 1,2,7-9, 12-15, 17, 19 and 20 under 35 U.S.C. § 112, first paragraph, enablement requirement. The applicant respectfully traverses the rejection.

The examiner states that the rejected claims are directed to subject matter that is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically the examiner states that the conclusion of lack of enablement is reached because the claims encompass treating an infected patient. The examiner acknowledges applicants' presentation of *in vitro* data demonstrating activity, but states that the evidence presented is insufficient to support a claim encompassing *in vivo* treatment of HIV. However, the examiner alleges that the skilled artisan would recognize that here is allegedly no correlation between *in vitro* and *in vivo* results, because an *in vitro* assay cannot duplicate the allegedly complex conditions of *in vivo* therapy, such as possible delayed or inadequate contact of drug with the target site; drug stability, half-life or clearance from the blood; possible drug inactivation *in vivo*; and target tissue drug uptake such that an large enough local drug concentration may be achieved at the target site. The examiner opines that is:

> "mere speculation with no evidence to support the contention that the in vitro studies of the specification of in vivo activity. Applicant has only shown cell culture data not treating infected patients or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would recognize and appreciate that there is no known correlation between in vitro and in vivo results because the artisan recognizes that an in vitro assay cannot duplicate the complex conditions of in vivo therapy."

As a preliminary matter, the examiner notes that the examiner has not cited any reference to support the sweeping statement that there is, in general, no correlation between *in vitro* and *in vivo* results. This absence of support is not surprising in view of the fact that the modern drug discovery process practiced by pharmaceutical companies is based upon initially conducting *in vitro* assays of compounds prior to conducting *in vivo* experiments and is premised upon the *in vitro* assays being predictive *in vivo* activity. While it may be true that factors such as pharmacokinetics may complicate the relationship between *in vivo* and *in vitro* activity, such that *some* experimentation may be required in order to achieve the desired results (for example to determining the optimum formulation, route of administration, dosing frequency, and the like), such experimentation is well within the ability of the skilled artisan, and not undue in view of what is typically involved in developing a marketable drug.

The examiner is respectfully reminded that he must accept statements regarding enablement absent reasons or evidence to contrary. While the examiner has raised possibilities regarding drug uptake and drug delivery, the examiner has not provided any reasons or evidence that these possibilities would in fact serve to prevent practice of the invention where the methods of the present invention are used for *in vivo* treatment.

The applicant cites an example where, contrary to the examiner's assertion, *in vitro* activity has actually been found to translate to *in vivo* activity in the context of treating HIV infection. The applicant provides herewith the manufacturer's prescribing information sheet for Enfuviritide (Fuzeon®), a United States Food and Drug Administration (FDA) approved drug for the treatment of HIV infection. A copy of a publication by Bianchi, *et al.*, in *Proc. Nat. Acad. Sci., USA*, **2005**, 102(36), 12903-08 is also provided.

Enfuviritide, like the compounds used in the methods of the present application, is a peptide. Bianchi, *et al.*, demonstrated that enfuviritide, as well as other peptides, showed activity in a single round HIV infectivity assay. Enfuviritide is active *in vivo* against HIV infection. Therefore, the *in vitro* activity shown by Bianchi, *et al.* correlates with *in vivo* human activity against human HIV infection. The *in vitro* infectivity assay described by Bianchi, *et al.*, is believed to be similar in principle to the *in vitro* infectivity assay described in the specification of the present application at p. 12, lines 12-28.

The claims under examination are limited to methods utilizing a peptide containing the PXP motif. As indicated above, the specification exemplifies a number of small PXP-containing peptides which have been shown to interfere with Vif-Vif interactions.

The rejection alleges that there is insufficient disclosure in the specification that the demonstrated *in vitro* prevention of multimerization of Vif would be effective in treating HIV *in vivo*. The specification describes the connection between Vif multimerization and Vif function in the life cycle of HIV. The applicants have shown that Vif proteins can form multimers *in vitro* (p. 30 line 14 - p. 32 line 2) as well as within a cell (p. 31 line 32-p. 32 line 23).

Vif protein is essential for viral replication and productive infection of peripheral blood mononuclear cells, macrophages and H9 T-cells (specification, page 32, lines 26-30, citing Gabuzda *et al.*, *J. Virol.* 66(11):6489-95, 1992; Blanc *et al.*, *Virology,* 193(1):186-92, 1993 and von Schwedler *et al.*, *J. Virol*, 67(8):4945-55). The applicants have also identified the site on the Vif-Vif protein that is responsible for multimerization (p. 31 lines 5-29), and, significantly, have shown that HIV-1 viruses with mutations at the Vif-Vif binding domain show dramatically decreased infectivity in an HIV-1 infectivity assay (p. 32 line 27-p. 33 line 18). Indeed, applicants have demonstrated that deletion of the Vif-Vif binding domain at amino acids 151-164 severely decreases Vif function in the viral life cycle. The Vif Δ151-164 mutant is unable to rescue the infectivity of *vif*-defective viruses generated from H9 T-cells (specification, page 33, lines 13-17).

The skilled artisan would expect, based on these results, that a compound that is capable of inhibiting Vif-Vif binding will be effective in reducing HIV infectivity in an HIV infectivity assay. As the references cited above demonstrate, activity of a compound in an HIV infectivity assay can be expected to correlate with the compound being efficacious against HIV *in vivo*, and therefore useful in the treatment of HIV infection. Thus, it is apparent from the specification that an agent that inhibits multimerization of the Vif protein would be effective in inhibiting the course of HIV infection.

The specification further provides compounds that are indeed effective in inhibiting the multimerization of the Vif protein, specifically peptides comprising the PXP motif. The specification demonstrates that the PXP motif-containing peptides SEQ ID NOs: 11, 13, 21, 22 and 23 are all capable of inhibiting the Vif-Vif interaction required for Vif multimerization.

Although the disclosure provided in the specification is itself sufficient, in view of the state of the art, to demonstrate enablement of the claimed invention, the applicant provides herewith yet further evidence of the enablement of the invention in the form of the Declaration of Dr Robert W. Buckheit (the "Buckheit Declaration"), providing direct evidence that PXP-motif-containing peptide Vif multimerization antagonists are indeed effective in inhibiting HIV

infectivity. As demonstrated above, *in vitro* inhibition of HIV infectivity correlates to *in vivo* efficacy versus HIV infection.

Applicant hereby informs the examiner, and places on the record, that the experiments described in the Buckheit declaration were carried out pursuant to a contract between ImQuest BioSciences and OyaGen Inc. OyaGen Inc. is a licensee of the present application from the assignee, Thomas Jefferson University. OyaGen engaged ImQuest Biosciences to perform the experiments described in the Buckheit Declaration.

The Buckheit Declaration describes further experiments with a peptide comprising the sequence SEQ ID NO:11. The peptide was shown to be active in an *in vitro* HIV infectivity assay. The tested peptide ("Peptide 2" in the Buckheit Declaration) comprised SEQ ID NO:11 linked to the TAT peptide. The specification contemplates such fusion peptides comprising PXP motif-containing peptides fused to any heterologous protein. See p. 21, lines 9-22; p. 23, lines 3-15.

The peptide comprising the sequence SEQ ID NO:11 was tested in an HIV-1 infection assay utilizing the MT2 cell line, an HTLV-1-transformed human lymphoblast line. Compound (the peptide comprising the sequence SEQ ID NO:11 or a control) was added to MT-2 cells in culture. The cells were infected with the laboratory adapted strain HIV-1_{IIIB} according to standard protocols. Virus replication in the infected MT-2 cells was monitored by reverse transcriptase assay. Compounds were tested at four different multiplicities of infection (MOIs). Except at the lowest MOI, the peptide comprising the sequence SEQ ID NO:11 suppressed viral replication, as determined by reverse transcriptase assay.

The HIV-1 infectivity data for the peptide comprising the sequence SEQ ID NO:11 confirms that peptides that inhibit Vif multimerization are effective in inhibiting viral replication, and therefore viral infectivity.

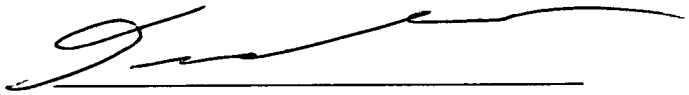
Based on the foregoing, the rejection under the enablement requirement is believed to have been overcome. The applicant therefore respectfully requests reconsideration and withdrawal of the rejection under the 35 U.S.C. § 112 paragraph 1 enablement requirement.

Conclusion

It is believed that the present response addresses all the issues raised by the examiner and places the application in condition for allowance. An early and favorable action toward that end is therefore respectfully and earnestly solicited.

Respectfully submitted,

HUI ZHANG, *et al.*



DANIEL A. MONACO
Registration No. 30,480
DRINKER BIDDLE & REATH LLP.
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
(215) 988-3312 - phone
(215) 988-2757 – Fax
Attorney for the Applicants